Package leaflet: Information for the user

Xiapex 0.9 mg powder and solvent for solution for injection
collagenase *clostridium histolyticum*

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xiapex is and what it is used for
2. What you need to know before you are given Xiapex
3. How Xiapex is used
4. Possible side effects
5. How to store Xiapex
6. Contents of the pack and other information

1. What Xiapex is and what it is used for

Xiapex may be used for the treatment of two different conditions: **Dupuytren's contracture in adult patients with a palpable cord** and **Peyronie's disease in adult men**.

- **Dupuytren's contracture**

This is a disease that causes your finger(s) to bend inward. This bending is called a contracture and is caused by the abnormal formation of a cord containing collagen under your skin. For many people, a contracture causes significant difficulties with performing everyday tasks like driving, shaking hands, playing sports, opening jars, typing or holding objects.

- **Peyronie's disease**

This is a condition where adult men have a 'plaque' that can be felt and a curve to their penis. The disease can cause a change in the shape of the erect penis due to the abnormal buildup of scar tissue, known as a plaque, within the stretchy fibres of the penis. The plaque may interfere with the ability to get a straight erection because the plaque will not stretch as much as the rest of the penis. Men with Peyronie's disease may have an erection that is curved or bent.

The active substance in Xiapex is collagenase *clostridium histolyticum*, and is naturally produced by a bacterium named *Clostridium histolyticum*. Xiapex is injected by your doctor into the cord in your finger/hand or plaque in your penis and works by breaking down the collagen in the cord or plaque. For Dupuytren's disease this thereby helps to remove the cause of your contracture so that your finger(s) can straighten.
For Peyronie's disease this may help break down the plaque that is causing your erect penis to curve, which may help the erection to be straighter and enable you to feel less bothered by your disease.

2. What you need to know before you are given Xiapex

You must not be given Xiapex:
- If you are allergic to collagenase *clostridium histolyticum* or any of the other ingredients of this medicine (listed in section 6).

- For Peyronie's disease if the treatment of your plaque involves the tube (called the urethra) that your urine passes through.

Warnings and precautions
Talk to your doctor or pharmacist before you are given Xiapex.

Allergic reactions
Severe allergic reactions can happen in patients who receive Xiapex, because it contains proteins foreign to the human body.

Call your doctor right away if you have any of these symptoms of an allergic reaction after an injection of Xiapex:
- hives
- swollen face
- breathing trouble
- chest pain

The potential for a serious allergic reaction or the development of a musculoskeletal syndrome upon repeated use of Xiapex cannot be excluded. The symptoms of musculoskeletal syndrome could be joint or muscle pain, shoulder stiffness, hand swelling, fibrosis of the palms, and thickening or nodule forming of tendons. If you notice such symptoms you should inform your doctor.

Before you are given this medicine, make sure your doctor knows:
- if you have had an allergic reaction to a previous Xiapex injection.
- if you have a history of problems with the normal clotting of your blood or if you are taking any medicines to help control the normal clotting of your blood (known as anticoagulation medicines).
- if you are currently taking any anticoagulation medicines, you must not receive Xiapex within 7 days of last dose of your anticoagulation medicine. One exception is the use of up to 150 mg daily dose of acetylsalicylic acid (a substance present in many medicines used to prevent blood clotting) which can be taken.
- if you have any other medical condition.

If you are treated for Dupuytren's contracture

This medicine must only be injected into the collagen cord in your hand by your doctor. Your doctor will take care to avoid injecting into tendons, nerves or blood vessels. Incorrect injection into tendons, nerves or blood vessels may result in bleeding or damage and possible permanent injury to these structures. If your cord to be treated is attached to the skin, you are at higher risk of the skin splitting or tearing during the finger extension procedure following the injection of Xiapex.

Tell your doctor if you have previously received or are thinking about receiving Xiapex to treat a condition known as Peyronie's disease. This condition affects adult men, who have a 'plaque' that can be felt and a curve to their erect penis.

If you are treated for Peyronie's disease

This medicine must only be injected into the plaque in your penis by your doctor.

Penile fracture (corporal rupture) or other serious injury to the penis
Receiving an injection of Xiapex may cause damage to the tubes in your penis called the corpora. After treatment with Xiapex, one of these tubes may break during an erection. This is called a corporal rupture or penile fracture.
After treatment with Xiapex, blood vessels in your penis may also break, causing blood to collect under the skin (which is called a haematoma).
Symptoms of penile fracture (corporal rupture) or other serious injury to your penis may include:
- a popping sound or sensation in an erect penis
- sudden loss of the ability to maintain an erection

- pain in your penis
- purple bruising and swelling of your penis
- difficulty urinating or blood in the urine

Call your doctor right away if you experience any of the symptoms of penile fracture or serious injury to your penis listed above.
Do not have sex or have any other sexual activity for at least 2 weeks after the second injection of a treatment cycle with Xiapex and after any pain and swelling has gone away.

Tell your doctor if you are thinking about receiving or have previously received Xiapex to treat a condition known as Dupuytren's contracture. In this condition, a cord forms in the tissue in the palm of the hand and causes one or more fingers to bend toward the palm so that they cannot be straightened.

Children and adolescents
There is no relevant use of Xiapex in children aged 0-18 years for the treatment of Dupuytren's contracture or Peyronie's disease.

Other medicines and Xiapex
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines to help control the normal clotting of your blood (known as anticoagulation medicines), anthraquinone derivatives, some antibiotics (tetracyclines and anthracyclines/anthraquinolones) used to treat infections and those medicines obtained without a prescription.

Pregnancy and breast-feeding
Dupuytren's contracture
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.
There is no experience in the use of Xiapex in pregnant women therefore the use of Xiapex is not recommended in pregnancy, and treatment should be postponed until after pregnancy.

There is no experience in the use of Xiapex in breast-feeding women therefore the use of Xiapex is not recommended during breast-feeding.

Peyronie's disease
This condition does not occur in females.

Driving and using machines
If you experience dizziness, numbness or altered sensation, and headache immediately after an injection of Xiapex you must avoid potentially hazardous tasks such as driving or using machines until these effects have passed or until advised by your doctor.

Swelling and pain may impair the use of the treated hand in Dupuytren's disease.

Xiapex contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially 'sodium- free'.

3. How Xiapex is used

You will be given Xiapex as an injection directly into the area that is causing your finger/penis to bend (intralesional injection). Your doctor will perform all injections of Xiapex.

The recommended dose of your prescribed medicine is 0.58 mg.

- **Dupuytren's contracture**

The total volume of the injection depends on the joint being treated. Your doctor will carefully select an area where the collagen cord is best accessible and will proceed with the injection into the cord.

After the injection, your doctor will place a dressing on your hand. You must limit motion of the treated finger for a day and it is not uncommon for the finger to straighten on its own for some patients. Until advised by your doctor, do not flex or extend the fingers of the injected hand. Do not attempt to disrupt the injected cord by self manipulation at any time. Elevate the injected hand as much as possible until the day after the finger extension procedure.

Your doctor will ask you to return the day after your injection to attempt to extend your finger to straighten it. Following extension of your finger, your doctor will fit you with a splint to wear at bedtime for up to 4 months.
If your finger is still not able to straighten during a follow-up visit with your doctor, you may need additional treatments with Xiapex which may be administered approximately 4 weeks after the first treatment. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals. Only one cord must be treated at a time. If the disease has resulted in multiple contractures, treatment of each cord must be undertaken in a sequential order, as determined by your doctor.

Be sure to ask your doctor when you can resume normal activities after treatment with Xiapex. It is recommended to avoid strenuous activities of your finger until instructed further by your doctor. Your doctor may recommend you perform a series of finger flexion and extension exercises several times a day for several months.

Clinical study experience with Xiapex is currently limited to up to 3 injections per cord and up to a total of 8 injections in the hands.

- **Peyronie's disease**

Your doctor will inject Xiapex into the plaque that is causing your penis to curve.

- Xiapex is given as part of a treatment cycle. In each treatment cycle, you will receive one injection of Xiapex, followed by a second injection on a separate day (1 to 3 days later).
- After each injection of Xiapex, your penis may be wrapped with a bandage. Your doctor will tell you when to remove the dressing.
- One to three days after the second injection of Xiapex in a treatment cycle, you will need to return to your doctor for a manual procedure that will help stretch and help straighten your penis. Your doctor will tell you when to come back for this.
- Your doctor will show you how to gently stretch and straighten your penis the right way. For further information see **"Instructions on how to gently stretch your penis"** and **"Instructions on how to gently straighten your penis" at the end of the Patient leaflet.**
- **You should only gently *stretch* your penis when you *do not have* an erection.** You should gently stretch your penis 3 times a day for 6 weeks after each treatment cycle.
- **You should only gently *straighten* your penis if you *have* an erection that happens without any sexual activity (spontaneous erection).** You should gently straighten your penis 1 time a day for 6 weeks after each treatment cycle.
- Your doctor will tell you when you can resume sexual activity after each treatment cycle.
- Your doctor will also tell you when to come back if more treatment cycles are needed.

Clinical study experience with Xiapex is currently limited to four treatment cycles in which a total of 8 injections may be administered into the plaque causing the curvature.

Tell your doctor right away if you have trouble stretching or straightening your penis, or if you have pain or other concerns.

If you receive more Xiapex than you should
As this product is administered to you by your doctor it is very unlikely that you will be given an incorrect dosage. In the unlikely event that your doctor administers a higher dosage than

recommended, you may experience an increase in the severity of possible side effects listed in section 4 “Possible Side Effects”.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reaction
Please consult a doctor immediately if you experience any signs or symptoms of a serious allergic reaction, e.g., wide spread redness or rash, swelling, tightness in the throat or difficulty breathing. **You must not be given Xiapex** if you know that you have had a serious allergic reaction to collagenase or any of the other ingredients.

- **Dupuytren’s contracture**

Most of the side effects that occurred in the clinical studies were mild or moderate in severity and were localised to the hand treated.

The following side effects have been seen with Xiapex:

Very common side effects (may affect more than 1 in 10 people):
- reactions at the injection site like bleeding, pain, swelling, tenderness and bruising
- itching in the hand
- feeling of pain in the hand, wrist or arm
- swollen or enlarged glands near the elbow or under the arm
- swelling in the hand or arm

Common side effects (may affect up to 1 in 10 people):
- reactions at the injection site like pain, warmth, swelling, presence of a blister, redness of skin and/or skin rash
- skin wound at the site of injection
- painful glands near the elbows or under the arm
- joint swelling and pain
- burning sensation, partial loss of sensitivity, feeling of “pins and needles” or numbness
- dizziness, headache, nausea
- increased perspiration

Uncommon side effects (may affect up to 1 in 100 people):
- rupture of a tendon, ligament injury
- low blood platelet count
- swelling of the eyelid
- allergic reaction
- chronic pain
- discomfort, injury, paralysis of the limb
- tremor/shaking
- fainting
- vomiting, diarrhoea, upper abdominal pain
- rash, eczema
- stiffness, creaking of the joints
- muscle spasm, muscle weakness, musculoskeletal stiffness or discomfort
- feeling of pain in the groin, shoulder, chest wall, or neck
- swelling

- fever, general pain, discomfort, tiredness, feeling hot, malaise, flu-like illness
- reactions at the site of injection including peeling of the skin, skin discoloration, infection, pain, skin tightness, numbness, irritation or nodules, scab, wound
- increased liver enzymes
- agitation, disorientation, irritability, restlessness, difficulty sleeping
- shortness of breath, hyperventilation
- inflammation of lymphatic channels (lymphangitis) leading to reddened skin with elevated borders, tender and warm, usually accompanied by a red streak, enlarged lymph nodes

- **Peyronie's disease**

Penile Fracture (corporal rupture) or other serious injury to the penis
Call your doctor right away if you experience any of the symptoms of penile fracture or other serious injury to your penis which are as follows: a popping sound or sensation in an erect penis, sudden loss of the ability to maintain an erection, pain in your penis, purple bruising and swelling of your penis, difficulty urinating or blood in the urine, a collection of blood under the skin at the injection site.

Most of the side effects that occurred in the clinical studies were mild or moderate in severity and most resolved within 2 weeks of the injection.

The following side effects have been seen with Xiapex:

Very common side effects (may affect more than 1 in 10 people)**:**
- bruising or swelling of the penis and pain in the penis
- a small collection of blood under the skin at the injection site

Common side effects (may affect up to 1 in 10 people)**:**
- reactions at the injection site such as presence of a blister, swelling, itching or a solid raised area under the skin
- pain at the injection site and above the penis
- blister or redness/discolouration of the penis
- genital itchiness
- painful erection, painful sex and erectile dysfunction.

Uncommon side effects (may affect up to 1 in 100 people)**:**
- lymph node pain and swollen lymph nodes
- increased white blood cells
- fast heart rate
- ringing in the ear
- abdominal swelling
- constipation
- feeling hot
- injection site rash
- fever
- weakness
- chills
- flu-like illness
- drainage from a blister on the penis
- tenderness
- allergic reaction
- fungal skin infection
- infection
- upper respiratory infection
- skin cut

- open wound
- collection of blood outside of a blood vessel on scrotum
- joint injury
- popping sound/sensation indicating penile fracture
- blood sugar increased
- blood pressure increased
- water retention
- back pain
- groin pain and discomfort
- thickening near ligament at base of penis
- tenderness in ligament at base of penis
- headache
- dizziness
- unpleasant taste
- abnormal sensation
- burning sensation
- increased/decreased sensitivity to stimuli to senses
- abnormal dreams
- depression
- avoidance of sex
- painful/increased urination
- scar tissue in penis
- penis disorder
- Peyronie's disease
- sexual dysfunction
- scrotal redness, swelling and pain
- genital discomfort and bruising
- pelvic pain
- penis size reduced
- formation of a blood clot inside the penile vein
- cough
- small area of inflammation
- night sweats
- sore on the skin of the penis
- skin rash producing redness
- skin disorder/irritation
- collection of blood outside the blood vessels
- bruising
- disease of the lymph vessels
- superficial vein inflammation

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the details below. By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard
Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517

Website: www.hpra.ie
e-mail: medsafety@hpra.ie

5. How to store Xiapex

Keep this medicine out of the sight and reach of children.

Your doctor must not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator at 2ºC-8ºC. Do not freeze.

After reconstitution, immediate use of the medicine is recommended. Reconstituted Xiapex can be kept at ambient room temperature (20ºC-25ºC) for up to one hour or refrigerated at 2ºC-8˚C for up to 4 hours prior to administration. If refrigerated, the reconstituted solution must be allowed to return to ambient room temperature (20ºC-25ºC) for approximately 15 minutes before use.

Your doctor must not use Xiapex if the reconstituted solution is discolored or contains particles. The solution must be clear, colourless with no lumps or flakes or particles.

Your doctor will take care of storing, handling and disposing of Xiapex. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicenes you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xiapex contains

- The active substance is collagenase *clostridium histolyticum*. Each vial of Xiapex contains 0.9 mg of collagenase *clostridium histolyticum.*
- The other ingredients are sucrose, trometamol and hydrochloric acid 2,4% w/w (for ph adjustment).
- The solvent contains calcium chloride dihydrate, sodium chloride and water for injections.

What Xiapex looks like and contents of the pack
Xiapex is a powder and solvent for solution for injection. The white lyophilised powder is supplied in a 3 ml type I clear glass vial with rubber stopper, aluminium seal and flip-off plastic cap.

The solvent that is used to dissolve the powder is a clear colourless liquid. 3 ml solution is supplied in a 5 ml type I clear glass vial with rubber stopper, aluminium seal and flip-off plastic cap.

Xiapex is supplied in a pack containing 1 vial of Xiapex powder and 1 vial of solvent.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden

Manufacturer
Swedish Orphan Biovitrum AB (publ), SE-112 76 Stockholm, Sweden

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

The following information is intended for Peyronie's disease patients only:

Instructions on how to gently stretch your penis

Gently stretch your penis 3 times a day. Only stretch your penis if your penis in not hard (erect).

- With one hand, hold the tip of your penis with your fingers. With the other hand, hold the base of your penis with the fingers (see illustration below).
- Gently pull your penis away from your body to its full length and hold the stretch for 30 seconds.
- Let go of the tip of your penis and let your penis return to its normal length.

Instructions on how to gently straighten your penis

Gently straighten your penis one time a day. Only straighten your penis if you have an erection that happens without any sexual activity (spontaneous erection). Bending your penis should not cause any pain or discomfort.

- With one hand hold your penis. With your other hand, gently bend your penis in the opposite direction of the curve (see illustration below). Hold the penis in this more straightened position for 30 seconds, then let go.

The following information is intended for healthcare professionals only:

Instructions for use and handling

Dupuytren's contracture

1. Preparation - Reconstitution procedure

The single dose vial containing Xiapex and the single dose vial containing the solvent for solution for injection for reconstitution must be refrigerated.

1. Before use, remove the vial containing the lyophilized powder of Xiapex and the vial containing the diluent for reconstitution from the refrigerator and allow the two vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Visually inspect the vial containing Xiapex. The cake of lyophilized powder should be intact and white in colour.

2. Confirm the joint to be treated (metacarpophalangeal [MP] or proximal interphalangeal [PIP]) as the volume of solvent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection).

3. After removal of the flip-off cap from each vial, using aseptic technique swab the rubber stopper and surrounding surface of the vial containing Xiapex and the vial containing the diluent for reconstitution with sterile alcohol (no other antiseptics should be used).

4. Use only the supplied diluent for reconstitution. The diluent contains calcium which is required for the activity of Xiapex.

5. Using a 1 ml syringe with 0.01 ml graduations with a 27-gauge 12-13 mm needle (not supplied), withdraw the correct volume of the **diluent supplied**:

- **0.39 ml of solvent for cords affecting a MP joint in Dupuytren's contracture**
- **0.31 ml of solvent for cords affecting a PIP joint in Dupuytren's contracture**

6. Inject the diluent slowly into the sides of the vial containing the lyophilized powder of Xiapex. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution.

7. The reconstituted Xiapex solution can be kept at room temperature (20º to 25ºC) for up to one hour or refrigerated at 2º to 8°C for up to 4 hours prior to administration. If the reconstituted Xiapex solution is refrigerated, allow this solution to return to room temperature for approximately 15 minutes before use.

8. Discard the syringe and needle used for reconstitution and the diluent vial.

2. Identification of treatment area

1. Prior to each treatment cycle, identify the treatment area as follows:
   Confirm the joint to be treated (metacarpophalangeal [MP] or proximal interphalangeal [PIP]) as the volume of solvent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection).

3. Injection procedure

Administration of a local anaesthetic medicinal product prior to injection of Xiapex is not recommended, as it may interfere with proper placement of the injection.

1. The reconstituted Xiapex solution should be clear. Inspect the solution visually for particulate matter and discoloration prior to administration. If the solution contains particulates, is cloudy, or is discoloured, do not inject the reconstituted solution.

2. Reconfirm the cord to be injected. The site chosen for injection must be the area where the contracting cord is maximally separated from the underlying flexor tendons and where the skin is not intimately adhered to the cord.

3. Apply antiseptic at the site of the injection and allow the skin to dry.

4. Using a new sterile, hubless syringe with 0.01 ml graduations and a permanently fixed, 26 or 27 gauge, 12 or 13 mm needle (not supplied), withdraw the adequate **volume of reconstituted solution** for a 0.58 mg dose of Xiapex required for injection to deliver:
   - **0.25 ml of reconstituted Xiapex for cords affecting a MP joint or**
   - **0.20 ml of reconstituted Xiapex for cords affecting a PIP joint.**

5. Use caution with cords as they approach the PIP flexion crease area. If injecting into a cord affecting the PIP joint of the fifth (little) finger, care must be taken to inject as close to the palmar digital crease as possible and not to insert more than 2 mm to 3 mm in depth. For PIP joints do not inject more than 4 mm distal to the palmar digital crease.

6. With your non-dominant hand, secure the patient's hand to be treated while simultaneously applying tension to the cord. With your dominant hand, place the needle into the cord, using caution to keep the needle within the cord. Avoid having the needle tip pass completely through the cord to help minimise the potential for injection of Xiapex into tissues other than the cord. After needle placement, if there is any concern that the needle is in the flexor tendon, apply a small amount of passive motion at the distal interphalangeal (DIP) joint. If insertion of the needle into a tendon is suspected or paresthesia is noted by the patient, withdraw the needle and reposition it into the cord. If the needle is in the proper location, there will be some resistance noted during the injection procedure. See Figure 1 below for an illustration of the injection technique.

7. After confirming that the needle is correctly placed in the cord, inject approximately one-third of the dose.

8. Next, keeping the needle under the skin at all times, withdraw the needle tip from the cord and reposition it in a slightly more distal location (approximately 2-3 mm) to the initial injection in the cord and inject another one-third of the dose.

9. Again keeping the needle under the skin at all times, withdraw the needle tip from the cord and reposition it a third time proximal to the initial injection (approximately 2-3 mm) and inject the final portion of the dose into the cord (see Figure 2).

The figures 1 and 2 below are for illustrative purposes only and may not be representative of the precise location of anatomical structures in an individual patient.

Figure 1: Illustration of the injection technique.

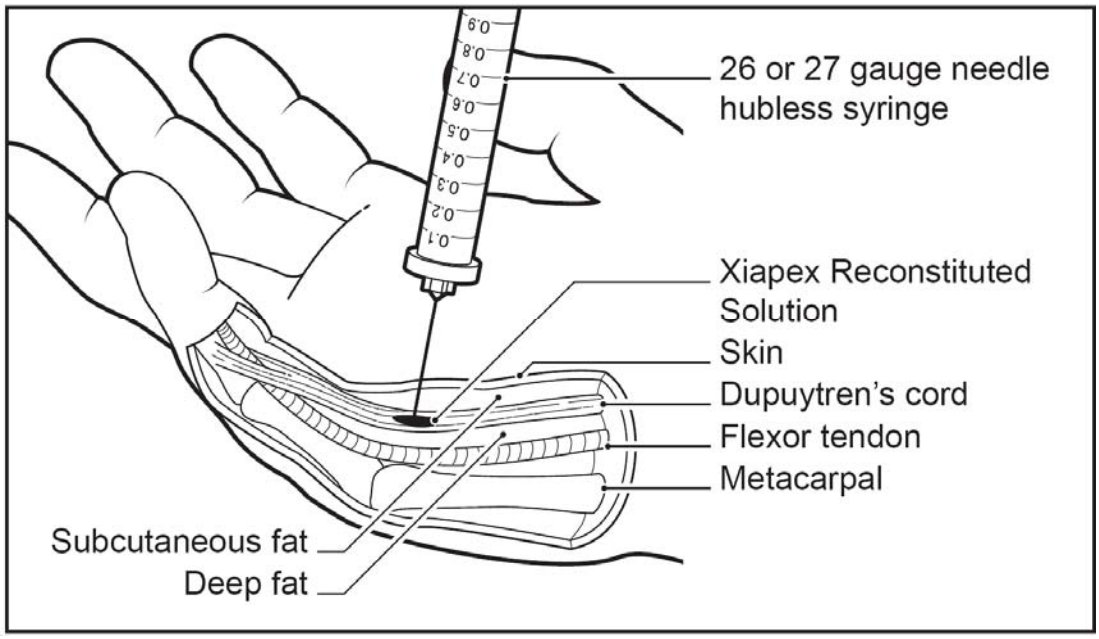
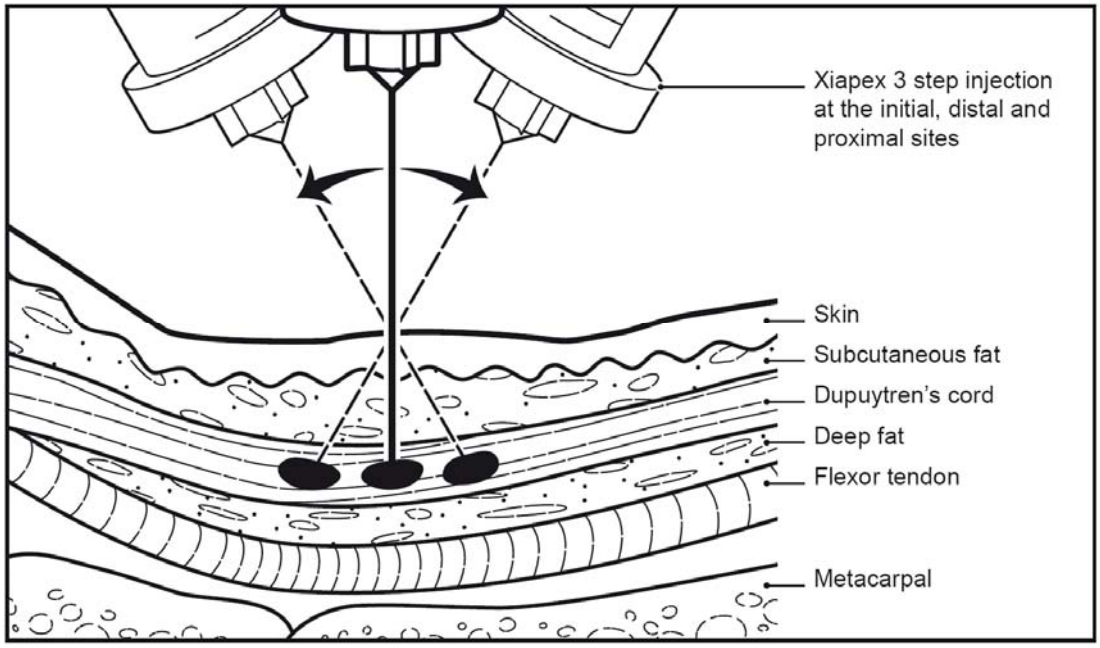


Figure 2: Three step injection of Xiapex into the cord.



10. Wrap the patient's treated hand with a soft, bulky, gauze dressing.

11. Discard the unused portion of the reconstituted solution and solvent after injection. Do not store, pool, or use any vials containing unused reconstituted solution or solvent.

12. Patients should be instructed:
    - Not to flex or extend the fingers of the injected hand to reduce extravasation of Xiapex out of the cord until the finger extension procedure is completed.
    - Not attempt to disrupt the injected cord by self manipulation at any time.
    - To elevate the injected hand as much as possible until the day after the finger extension procedure.

- To promptly contact their doctor if there is evidence of infection (e.g., fever, chills, increasing redness or oedema) or trouble bending the finger after the swelling goes down (symptoms of tendon rupture).
- To return to see their physician the next day for an examination of the injected hand and a possible finger extension procedure to disrupt the cord.

4. Finger extension procedure

1. At the follow-up visit the day after injection, determine if the contracture has resolved. If a cord contracture remains, a passive finger extension procedure will be performed in an attempt to disrupt the cord.

2. Local anaesthesia may be used, if needed, during the finger extension procedure.

3. While the patient's wrist is in the flexed position, apply moderate stretching pressure to the injected cord by extending the finger for approximately 10 to 20 seconds. For cords affecting the PIP joint, perform the finger extension procedure when the MP joint is in the flexed position.

4. If the first finger extension procedure does not result in disruption of the cord, a second and third attempt can be performed at 5- to 10-minute intervals. No more than 3 attempts are recommended to disrupt a cord.

5. If the cord has not disrupted after 3 attempts of extension, a follow-up visit may be scheduled approximately 4 weeks after the injection. If, at that subsequent visit the contracted cord persists, an additional injection and finger extension procedure may be performed.

6. Following the finger extension procedure(s) and fitting patient with a splint (with treated joint in maximum extension), patients should be instructed to:
   - Not perform strenuous activity with the injected hand until advised to do so.
   - Wear the splint at bedtime for up to 4 months.
   - Perform a series of finger flexion and extension exercises several times a day for several months.

The following information is intended for healthcare professionals only:

Instructions for use and handling

<u>Peyronie's disease</u>

1. Preparation - Reconstitution procedure

The single dose vial containing Xiapex and the single dose vial containing the solvent for solution for injection for reconstitution must be refrigerated.

a) Before use, remove the vial containing the lyophilized powder of Xiapex and the vial containing the diluent for reconstitution from the refrigerator and allow the two vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Visually inspect the vial containing Xiapex. The cake of lyophilized powder should be intact and white in colour.

b) After removal of the flip-off cap from each vial, using aseptic technique swab the rubber stopper and surrounding surface of the vial containing Xiapex and the vial containing the diluent for reconstitution with sterile alcohol (no other antiseptics should be used).

c) Use only the supplied diluent for reconstitution. The diluent contains calcium which is required for the activity of Xiapex.

d) Using a 1 ml syringe with 0.01 ml graduations with a 27-gauge 12-13 mm needle (not supplied), withdraw the correct volume of the **diluent supplied**:

- **<u>0.39 ml of solvent for the penile plaque in Peyronie's disease</u>**

e) Inject the diluent slowly into the sides of the vial containing the lyophilized powder of Xiapex. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution.

f) The reconstituted Xiapex solution can be kept at room temperature (20º to 25ºC) for up to one hour or refrigerated at 2º to 8°C for up to 4 hours prior to administration. If the reconstituted Xiapex solution is refrigerated, allow this solution to return to room temperature for approximately 15 minutes before use.

g) Discard the syringe and needle used for reconstitution and the diluent vial.

2. Identification of treatment area

a) Prior to each treatment cycle, identify the treatment area as follows:
- Induce a penile erection
- Locate the plaque at the point of maximum concavity (or focal point) in the bend of the penis
- Mark the point with a surgical marker. This indicates the target area in the plaque for Xiapex deposition

3. Injection procedure

a) The reconstituted Xiapex solution should be clear. Inspect the solution visually for particulate matter and discoloration prior to administration. If the solution contains particulates, is cloudy, or is discoloured, do not inject the reconstituted solution.

b) Apply antiseptic at the site of the injection and allow the skin to dry.

c) Administer suitable local anesthetic, if desired.

d) Using a new hubless syringe containing 0.01 ml graduations with a permanently fixed 27-gauge 12 or 13 mm needle (not supplied), withdraw a volume of 0.25 ml of **reconstituted solution (containing 0.58 mg of Xiapex).**

e) The penis should be in a flaccid state before Xiapex is injected. Place the needle tip on the side of the target plaque in alignment with the point of maximal concavity. Orient the needle so that it enters the plaque from the side, NOT downwards or perpendicularly towards the corpora cavernosum.

f) Insert and advance the needle transversely through the width of the plaque, towards the opposite side of the plaque without passing completely through it. Proper needle position is tested and confirmed by carefully noting resistance to minimal depression of the syringe plunger.

g) With the tip of the needle placed within the plaque, initiate injection, maintaining steady pressure to slowly inject the drug into the plaque. Withdraw the needle slowly so as to deposit the full dose along the needle track within the plaque. For plaques that are only a few millimeters in width, the distance of withdrawal of the syringe may be very minimal. The goal is always to deposit the full dose entirely within the plaque.

h) Upon complete withdrawal of the needle, apply gentle pressure at the injection site. Apply a dressing as necessary.

i) Discard the unused portion of the reconstituted solution and diluent after each injection. Do not store, pool, or use any vials containing unused reconstituted solution or diluent.

j) The second injection of each treatment cycle should be made approximately 2 to 3 mm apart from the first injection.

4. Penile modeling procedure

Penile modeling helps relieve curvature deformity and straighten the penile shaft. At a follow-up visit 1 to 3 days after the second injection of each treatment cycle, perform a penile modeling procedure (as described below) on the flaccid penis to stretch and elongate the plaque that Xiapex has disrupted:

- Administer suitable local anaesthetic, if desired.
- Wearing gloves, grasp the plaque or indurated portion of the flaccid penis about 1 cm proximal and distal to the injection site. Avoid direct pressure on the injection site.
- Using the target plaque as a fulcrum point, use both hands to apply firm, steady pressure to elongate and stretch the plaque. The goal is to gradually create bending opposite to the patient’s penile curvature, with stretching to the point of moderate resistance. Hold pressure for 30 seconds then release.
- After a 30 second rest period, repeat the penile modeling technique for a total of 3 modeling attempts at 30 seconds for each attempt.

The patient should then be instructed to self-perform penile modeling activities at home each day for the 6- week period following the physician penile plaque modeling visit of each treatment cycle, according to the detailed instructions provided in the package leaflet.